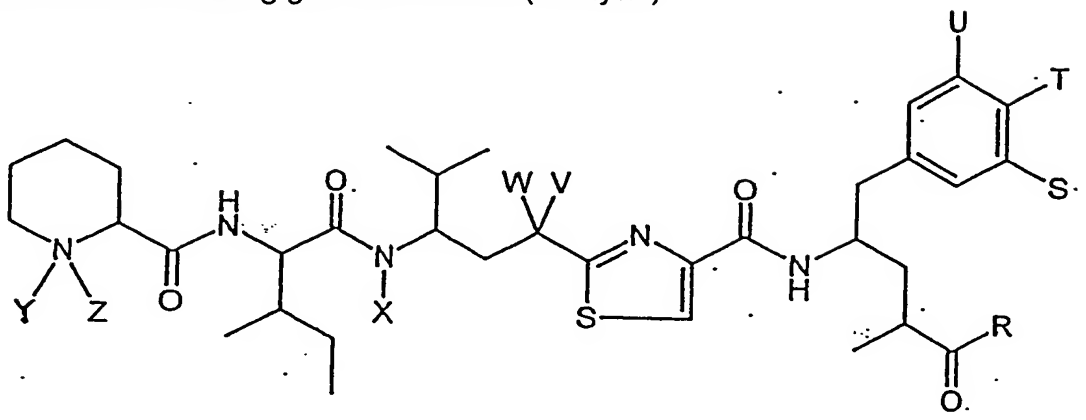
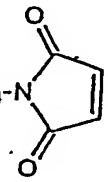
Patent claims

1. Compound of the following general formula I (tubulysin):



R, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, S, T, U, V, W, X, Y and Z having the following meanings:

R = H, alkyl, aryl, OR^1, NR^1R^2 or NH-$(CH_2)_{2-4}$- 

R^1 = H, alkyl or aryl

R^2 = H, alkyl or aryl

S = H, Hal, NO_2 or NHR^3

U = H, Hal, NO_2 or NHR^3

R^3 = H, HCO or alkyl-CO

T = H or OR^4

R^4 = H, alkyl, aryl, COR^5, $P(O)(OR^6)_2$ or SO_3R^6

R^5 = alkyl, alkenyl, aryl or heteroaryl

R^6 = H, alkyl or a metal ion

V = H, OR^7, Hal or (with W = O) O

R^7 = H, alkyl or COR^8

R^8 = alkyl, alkenyl or aryl

W = H or alkyl or (with V) O

X = H, alkyl, alkenyl or CH_2OR^9

R^9 = H, alkyl, alkenyl, aryl or COR^{10}

R^{10} = alkyl, alkenyl, aryl or heteroaryl

Y = (for Z = CH_3 or COR^{11}) free electron pair or (for Z = CH_3) O

R^{11} = alkyl, CF_3 or aryl and/or

Z = (for Y = O or free electron pair) CH_3 or (for Y = free electron pair) COR^{11}.

2. Compound according to claim 1, wherein

R, R^1, R^4, R^5, R^8, R^9, R^{10} and/or R^{11} = unsubstituted or substituted phenyl, especially C_{1-4}alkyl-substituted phenyl

R^5 = C_{1-4}alkyl, C_{2-6}alkenyl or pyridyl

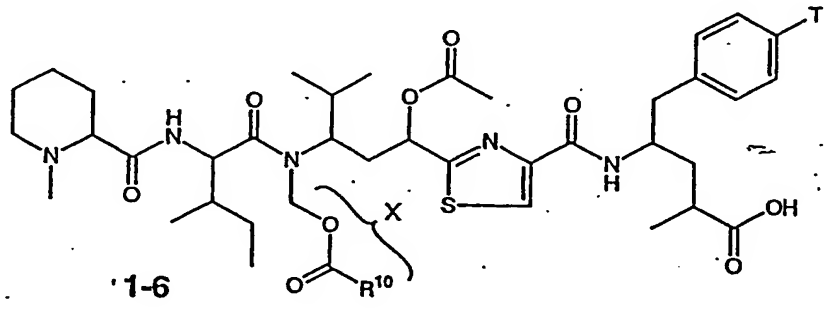
R^5 and/or X = C_{2-4}alkenyl

R^6 = an alkali metal ion, especially the Na ion, or an alkaline earth metal ion

R^8 and/or R^9 = C_{2-4}alkenyl and/or

R^{10} = C_{2-6}alkenyl, especially C_{2-4}alkenyl, or pyridyl.

3. (Scheme 1) Process for the preparation of a compound of the general formula I according to claim 1 (type 7) wherein R = OR^1, R^1 = H, S = U = H, T = H or OH, V = OR^7, R^7 = COR^8, R^8 = alkyl, preferably C_{1-4}alkyl, especially methyl, W = H, X = CH_2OR^9, R^9 = H, Y = free electron pair and Z = CH_3, in which process a compound of the following general formula II (type 1, 2, 3, 4, 5 or 6):



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wherein X = CH_2OR^9, R^9 = COR^{10}, R^{10} = alkyl, especially C_{1-6}alkyl, and which otherwise has the meanings indicated above is subjected to ester cleavage in an acidic medium and the compound of the general formula according to claim 1 having the indicated meanings is obtained.

4. Process according to claim 3, wherein the ester cleavage is carried out in an organic solvent, especially dioxane, in the presence of an acid, especially hydrogen chloride, and/or at elevated temperature.

5. (Scheme 1) Process for the preparation of a compound of the general formula according to claim 1 (type 8) wherein R = OR^1, R^1 = H, S = U = H, T = H or OH, V = OR^7, R^7 = COR^8, R^8 = alkyl, preferably C_{1-4}alkyl, especially methyl, W = H, X = H, Y = free electron pair and Z = CH_3, in which process a compound of the general formula according to claim 3 (type 1, 2, 3, 4, 5 or 6) wherein X = CH_2OR^9, R^9 = COR^{10}, R^{10} = alkyl, preferably C_{1-6}alkyl, and which otherwise has the meanings indicated above is subjected to acetal cleavage and the compound of the general formula I according to claim 1 having the indicated meanings is obtained.

6. Process according to claim 5, wherein the acetal cleavage is carried out in an acidic medium, especially in the presence of hydrochloric acid, and/or at elevated temperature.

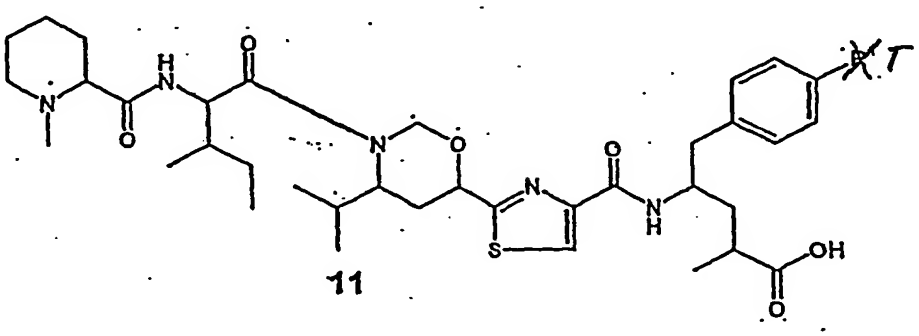
7. (Scheme 1) Process for the preparation of a compound of the general formula according to claim 1 (type 9) wherein R = OR^1, R^1 = H, S = U = H, T = H or OH, V = OR^7, R^7 = H, W = H, X = CH_2OR^9, R^9 = COR^{10}, R^{10} = alkyl, especially C_{1-6}alkyl, Y = free electron pair and Z = CH_3, in which process a compound of the general formula II according to claim 3 (type 1, 2, 3, 4, 5 or 6) wherein V = OR^7, R^7 = COR^8, R^8 = alkyl, preferably C_{1-4}alkyl, especially methyl, and which otherwise has the meanings indicated above is subjected to ester cleavage in a weakly alkaline medium and the compound of the general formula I according to claim 1 having the indicated meanings is obtained.

8. Process according to claim 7, wherein the ester cleavage is carried out in an organic medium, especially a hydrophilic organic solvent, preferably an alcohol, especially methanol, in the presence of a weak base, especially NH_3.

9. (Scheme 1) Process for the preparation of a compound of the general formula according to claim 1 (type 10) wherein R = OR^1, R^1 = H, S = U = H, T = H or OH, V = OR^7, R^7 = H, W = H, X = H, Y = free electron pair and Z = CH_3, in which process a compound of the general formula according to claim 3 (type 1, 2, 3, 4, 5 or 6) wherein V = OR^7, R^7 = COR^8, R^8 = alkyl, preferably C_{1-4}alkyl, especially methyl, X = CH_2OR^9, R^9 = COR^{10}, R^{10} = alkyl, especially C_{1-6}alkyl, and which otherwise has the meanings indicated above is subjected to double ester cleavage in a strongly alkaline medium and the compound of the general formula according to claim 1 having the indicated meanings is obtained.

10. Process according to claim 9, wherein the double ester cleavage is carried out in an organic medium, especially in a hydrophilic organic solvent, preferably an alcohol, especially methanol, in the presence of a strong base, especially an alkali metal hydroxide, preferably sodium hydroxide.

11. (Scheme 1) Process for the preparation of a compound of the following general formula III (type 11):



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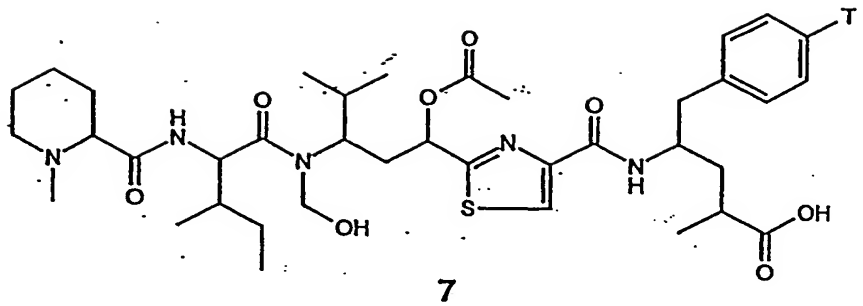
wherein R = OR^1, R^1 = H, S = U = H, T = H or OR^4, R^4 = H, V with X = CH_2O bridge, W = H, Y = free electron pair and Z = CH_3 in the general formula according to claim 1, in which process a compound of the general formula according to claim 3 (type 1, 2, 3, 4, 5 or 6) wherein X = CH_2OR^9, R^9 = COR^{10}, R^{10} = alkyl, especially C_{1-6}alkyl, V = OR^7, R^7 = COR^8, R^8 = alkyl, preferably C_{1-4}alkyl, especially methyl, and which otherwise has the meanings indicated above is subjected to ring formation with double ester cleavage in an acidic medium and the compound of the general formula above having the indicated meanings is obtained.

12. Process according to claim 12, wherein the ring formation is carried out in an aqueous medium, in the presence of an inorganic acid, preferably hydrochloric acid, and with heating.

13. (Scheme 2) Process for the preparation of a compound of the general formula according to claim 1 (type 12) wherein R = OR^1, R^1 = H, S = U = H, T = H or OR^4, R^4 = COR^5, R^5 = alkyl, especially C_{1-6}alkyl, alkenyl, especially C_{2-6}alkenyl, aryl or heteroaryl, V = OR^7, R^7 = COR^8, R^8 = alkyl, preferably C_{1-4}alkyl, especially methyl, W = H, X = CH_2OR^9, R^9 = COR^{10}, R^{10} = R^5, Y = free electron pair and Z = CH_3, in which process a compound of the following general formula IV (type 7):



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wherein X = CH_2OR^9, R^9 = H and which otherwise has the meanings indicated above is subjected to acylation and a compound of the general formula according to claim 1 having the indicated meanings is obtained.

14. Process according to claim 13, wherein the acylation is carried out using an acyl halide, especially an acyl chloride, and/or in the presence of a weak base, especially a weak organic base, preferably a tertiary amine, especially triethylamine.

15. (Scheme 2) Process for the preparation of a compound of the general formula according to claim 1 (type 13) wherein R = OR^1, R^1 = H, S = U = H, T = H or OR^4, R^4 = H, V = OR^7, R^7 = COR^8, R^8 = alkyl, preferably C_{1-4}alkyl, especially methyl, W = H, X = CH_2OR^9, R^9 = COR^{10}, R^{10} = alkyl, especially C_{1-6}alkyl, alkenyl, especially C_{2-6}alkenyl, aryl or heteroaryl, Y = free electron pair and Z = CH_3, in which process hydrolysis is carried out in an alkaline medium on a product of the process according to claim 13 wherein T = OR^4, R^4 = COR^5 and R^5 = alkyl, especially C_{1-6}alkyl, alkenyl, especially C_{2-6}alkenyl, aryl or heteroaryl and which otherwise has the meanings indicated above, and a compound of the general formula according to claim 1 having the indicated meanings is obtained.

16. Process according to claim 15, wherein the hydrolysis is carried out using ammonia.

17. (Scheme 3) Process for the preparation of a compound of the general formula according to claim 1 (type 14) wherein R = OR^1, R^1 = H, S = U = H, T = H or OH, V = OR^7, R^7 = COR^8, R^8 = alkyl, preferably C_{1-4}alkyl, especially methyl, W = H, X = CH_2OR^9, R^9 = alkyl, especially C_{1-4}alkyl, alkenyl or aryl, Y = free electron pair and Z = CH_3, in which process a starting compound of the process according to claim 3 (type 1, 2, 3, 4, 5 or 6) is subjected to ester cleavage and is alkylated and a compound of the general formula according to claim 1 having the indicated meanings is obtained.

18. Process according to claim 17, wherein the reaction is carried out using an alkylating agent of formula R^9OH wherein R^9 = alkyl, especially C_{1-4}alkyl, alkenyl or aryl.

19. Process according to claim 17 or 18, wherein the reaction is carried out in the presence of p-CH_3-$C_6H_4SO_2OH$ in tetrahydrofuran (THF) at elevated temperature.

20. (Scheme 4) Process for the preparation of a compound of the general formula according to claim 1 (type 15) wherein R = OR^1, R^1 = H, S = U = H, T = H or OR^4, R^4 = H, V = OR^7, R^7 = H or COR^8, R^8 = alkyl, preferably C_{1-4}alkyl, especially methyl, W = H, X = CH_3, Y = free electron pair and Z = CH_3, in which process a product of the process according to claim 3 (type 7) wherein X = CH_2OR^9, R^9 = H and which otherwise has the meanings indicated above is subjected to reduction and the compound of the general formula according to claim 1 having the indicated meanings is obtained.

21. Process according to claim 20, wherein the reduction is carried out using $NaCNBH_3$ and trifluoroacetic acid in methanol (MeOH).

22. (Scheme 4) Process for the preparation of a compound of the general formula according to claim 1 (type 15) wherein R = OR^1, R^1 = H, S = U = H, T = H or OR^4, R^4 = H, V = OR^7, R^7 = H or COR^8, R^8 = alkyl, especially C_{1-4}alkyl, especially methyl, W = H, X = CH_3, Y = free electron pair and Z = CH_3, in which process a compound of the general formula according to claim 11 (type 11) is subjected to ring opening with reduction or to reduction with ring opening and a compound of the general formula according to claim 1 having the indicated meanings is obtained.

23. Process according to claim 20, wherein the reaction is carried out in the presence of $NaCNBH_3$ in acetonitrile and, Me_3SiCl and (CH_3CN).

24. (Scheme 5) Process for the preparation of a compound of the general formula according to claim 1 (type 16) wherein R = OR^1, R^1 = H, S = U = H, T = H or OH, V = OR^7, R^7 = COR^8, R^8 = alkyl, especially C_{1-4}alkyl, alkenyl or aryl, W = H, X = CH_2OR^9, R^9 = COR^{10}, R^{10} = alkyl, especially C_{1-6}alkyl, or alkenyl, Y = free electron pair and Z = CH_3, in which process a product of a process according to claim 7 (type 9) wherein V = OR^7 and R^7 = H and which otherwise has the meanings indicated above is subjected to acylation

and the compound of the general formula according to claim 1 having the indicated meanings is obtained.

25. Process according to claim 24, wherein the acylation is carried out using an acyl halide of formula R^8COCl wherein R^8 = alkyl, especially C_{1-4}alkyl, alkenyl or aryl, especially an acyl chloride, and/or in the presence of a base, especially an organic base, preferably a trialkylamine, especially triethylamine.

26. (Scheme 5) Process for the preparation of a compound of the general formula according to claim 1 (type 17) wherein R = OR^1, R^1 = H, S = U = H, T = H or OR^4, R^4 = H, V = H or F, W = H, X = CH_2OR^9, R^9 = COR^{10}, R^{10} = alkyl, especially C_{1-6}alkyl, or alkenyl, Y = free electron pair and Z = CH_3, in which process a product of a process according to claim 7 (type 9) wherein V = OR^7 and R^7 = H and which otherwise has the meanings indicated above is subjected to catalytic hydrogenation or fluorination and the compound of the general formula according to claim 1 having the indicated meanings is obtained.

27. Process according to claim 26, wherein, for V = H, the hydrogenation is carried out using palladium-on-carbon in the presence of acetic acid and, for V = F, the fluorination is carried out using DAST in tetrahydrofuran.

28. (Scheme 5) Process for the preparation of a compound of the general formula according to claim 1 (type 18) wherein R = OR^1, R^1 = H, S = U = H, T = H or OR^4, R^4 = H, V with W = O, X = CH_2OR^9, R^9 = COR^{10}, R^{10} = alkyl, especially C_{1-6}alkyl, or alkenyl, Y = free electron pair and Z = CH_3, in which process a product of a process according to claim 7 (type 9) wherein V = OR^7 and R^7 = H and which otherwise has the meanings indicated above is subjected to oxidation with formation of a ketone and a compound of the general formula according to claim 1 having the indicated meanings is obtained.

29. Process according to claim 28, wherein the oxidation is carried out in the presence of TPAP and in dichloromethane NMO.

30. (Scheme 5) Process for the preparation of a compound of the general formula according to claim 1 (type 19) wherein R = OR^1, R^1 = H, S = U = H, T = H or OH, V = OR^7, R^7 = H, W = alkyl, especially C_{1-4}alkyl, X = CH_2OR^9, R^9 = COR^{10}, R^{10} = alkyl, especially C_{1-6}alkyl, or alkenyl, Y = free electron pair and Z = CH_3, in which process a product of a

process according to claim 28 or 29 (type 18) is reacted with a Grignard compound to form the compound of the general formula according to claim 1 having the indicated meanings.

31. Process according to claim 30, wherein the reaction is carried out using an organomagnesium compound of formula WMgHal wherein W = alkyl and especially C_{1-4}alkyl.

32. (Scheme 5) Process for the preparation of a compound of the general formula according to claim 1 (type 19) wherein R = OR^1, R^1 = H, S = U = H, T = H or OH, V = OR^7, R^7 = H, W = alkyl and especially C_{1-4}alkyl, X = CH_2OR^9, R^9 = COR^{10}, R^{10} = alkyl, especially C_{1-6}alkyl, or alkenyl, Y = free electron pair and Z = CH_3, in which process
(i) in a first step a process according to claim 28 or 29 is carried out and then
(ii) in a second step a process according to claim 30 or 31 is carried out and a compound of the general formula according to claim 1 having the indicated meanings is obtained.

33. (Scheme 6) Process for the preparation of a compound of the general formula according to claim 1 (type 20) wherein R = OR^1, R^1 = alkyl, especially C_{1-4}alkyl, or alkenyl, S = U = H, T = H or OR^4, R^4 = H, V = OR^7, R^7 = COR^8, R^8 = alkyl, preferably C_{1-4}alkyl, especially methyl, W = H, X = CH_2OR^9, R^9 = COR^{10}, R^{10} = alkyl, especially C_{1-6}alkyl, alkenyl, especially C_{2-6}alkenyl, aryl or heteroaryl, Y = free electron pair and Z = CH_3, in which process a starting compound of a process according to claim 3 (type 1, 2, 3, 4, 5 or 6) or a product of a process according to claim 15 (type 13) is subjected to alkylation or alkenylation and a compound of the general formula according to claim 1 having the indicated meanings is obtained.

34. Process according to claim 33, wherein the alkylation or alkenylation is carried out in the presence of EDC, R^1OH wherein R^1 = alkyl, especially C_{1-4}alkyl, or alkenyl, and DMAP in methylene chloride.

35. (Scheme 6) Process for the preparation of a compound of the general formula according to claim 1 (type 21) wherein R = NHR^1, NH-NR^1R^2, $NHOR^1$ or $NH(CH_2)_{2-4}NR^1R^2$, R^1 and R^2 each independently of the other = H, alkyl, especially C_{1-6}alkyl, or aryl, S = U = H, T = H or OR^4, R^4 = H, V = OR^7, R^7 = COR^8, R^8 = alkyl, preferably C_{1-4}alkyl, especially methyl, W = H, X = CH_2OR^9, R^9 = COR^{10}, R^{10} = alkyl, especially C_{1-6}alkyl, alkenyl, especially C_{2-6}alkenyl, aryl or heteroaryl, Y = free electron pair and Z = CH_3, in which

process a starting compound of a process according to claim 3 (type 1, 2, 3, 4, 5 or 6) or a product of a process according to claim 15 (type 13) is subjected to amination using a compound of formula RH, R having the indicated meanings, and a compound of the general formula according to claim 1 having the indicated meanings is obtained.

36. Process according to claim 35, wherein the reaction is carried out
(i) in the presence of EDC in methylene chloride or
(ii) in the presence of isobutyl chloroformate and triethylamine in THF.

37. (Scheme 6) Process for the preparation of a compound of the general formula according to claim 1 (type 22) wherein R = alkyl, especially C_{1-4}alkyl, or alkenyl, S = U = H, T = H or OR^4, R^4 = H, V = OR^7, R^7 = COR^8, R^8 = alkyl, preferably C_{1-4}alkyl, especially methyl, W = H, X = CH_2OR^9, R^9 = COR^{10}, R^{10} = alkyl, especially C_{1-6}alkyl, alkenyl, especially C_{2-6}alkenyl, aryl or heteroaryl, Y = free electron pair and Z = CH_3, in which process a starting compound of a process according to claim 3 (type 1, 2, 3, 4, 5 or 6) or a product of a process according to claim 15 (type 13) is reacted with an organolithium compound of formula RLi having the indicated meaning for R to form the compound of the general formula according to claim 1 having the indicated meanings.

38. (Scheme 6) Process for the preparation of a compound of the general formula according to claim 1 (type 23) wherein R = amino radical of 1-(2-amino-C_{2-4}alkyl)-pyrrole-2,5-dione, S = U = H, T = H or OR^4, R^4 = H, V = OR^7, R^7 = COR^8, R^8 = alkyl, preferably C_{1-4}alkyl, especially methyl, W = H, X = CH_2OR^9, R^9 = COR^{10}, R^{10} = alkyl, especially C_{1-6}alkyl, alkenyl, especially C_{2-6}alkenyl, aryl or heteroaryl, Y = free electron pair and Z = CH_3, in which process a starting compound of a process according to claim 3 (type 1, 2, 3, 4, 5 or 6) or a product of a process according to claim 15 (type 13) is subjected to amination using 1-(2-amino-C_{2-4}alkyl)-pyrrole-2,5-dione and the compound of the general formula according to claim 1 having the indicated meanings is obtained.

39. Process according to claim 38, wherein the amination is carried out in the presence of EDC in methylene chloride.

40. (Scheme 7) Process for the preparation of a compound of the general formula according to claim 1 (type 24) wherein R = OR^1, R^1 = H, S = U = H, T = OR^4, R^4 = $P(O)(OR^6)_2$ wherein R^6 = H or alkyl, especially C_{1-4}alkyl, or R^4 = SO_3R^6 wherein R^6 = H, V =

OR^7, $R^7 = COR^8$, R^8 = alkyl, preferably C_{1-4}alkyl, especially methyl, W = H, $X = CH_2OR^9$, $R^9 = COR^{10}$, R^{10} = alkyl, especially C_{1-6}alkyl, alkenyl, especially C_{2-6}alkenyl, aryl or heteroaryl, Y = free electron pair and $Z = CH_3$, in which process
(i) a starting compound (type 1, 2 or 3) according to claim 3 or
(ii) a product of a process according to claim 15 (type 13)
is reacted with
(a) a compound of formula $P(O)(OR^6)_2OH$ wherein R^6 = H or alkyl, especially C_{1-4}alkyl, or
(b) SO_3
and the compound of the general formula according to claim 1 having the indicated meanings is obtained.

41. Process according to claim 40, wherein the variant (a) is carried out in the presence of I_2 and pyridine in methylene chloride.

42. Process according to claim 40, wherein the variant (b) is carried out using pyridine-SO_3.

43. (Scheme 7) Process for the preparation of a compound of the general formula according to claim 1 (type 25) wherein $R = OR^1$, R^1 = H, S = U = H, $T = OR^4$, $R^4 = COR^5$, R^5 = alkyl, especially C_{1-4}alkyl, alkenyl or $N(R^{12})_2$, R^{12} = alkyl, $V = OR^7$, $R^7 = COR^8$, R^8 = alkyl, preferably C_{1-4}alkyl, especially methyl, W = H, $X = CH_2OR^9$, $R^9 = COR^{10}$, R^{10} = alkyl, especially C_{1-6}alkyl, alkenyl, especially C_{2-6}alkenyl, aryl or heteroaryl, in which process
(i) a starting compound (type 1, 2 or 3) according to claim 3 or
(ii) a product of a process according to claim 15 (type 13)
is subjected to acylation and the compound of the general formula according to claim 1 having the indicated meanings is obtained.

44. Process according to claim 43, wherein the acylation is carried out using an acyl halide of formula R^5COCl wherein R^5 = alkyl, especially C_{1-4}alkyl, alkenyl or $N(R^{12})_2$ and R^{12} = alkyl, especially using an acyl chloride, in the presence of an organic base, especially a trialkylamine, preferably triethylamine, in an organic solvent, especially THF.

45. (Scheme 7) Process for the preparation of a compound of the general formula according to claim 1 (type 26) wherein $R = OR^1$, R^1 = alkyl, especially C_{1-4}alkyl, or alkenyl, S = U = H, $T = OR^4$, R^4 = alkyl, especially C_{1-4}alkyl, or alkenyl, $V = OR^7$, $R^7 = COR^8$, R^8 =

alkyl, preferably C_{1-4}alkyl, especially methyl, W = H, X = CH_2OR^9, R^9 = COR^{10}, R^{10} = alkyl, especially C_{1-6}alkyl, alkenyl, especially C_{2-6}alkenyl, aryl or heteroaryl, Y = free electron pair and Z = CH_3, in which process
(i) a starting compound (type 1, 2 or 3) according to claim 3 or
(ii) a product of a process according to claim 15 (type 13)
is subjected to alkylation and the compound of the general formula according to claim 1 having the indicated meanings is obtained.

46. Process according to claim 45, wherein the alkylation is carried out using an alkyl iodide of formula R^4I wherein R^4 = alkyl, especially C_{1-4}alkyl, or alkenyl in the presence of a weak base, especially Ag_2O, in an organic solvent, especially methylene chloride.

47. Process according to claim 45, wherein methylation is carried out using diazomethane in an organic solvent, especially methanol.

48. (Scheme 7) Process for the preparation of a compound of the general formula according to claim 1 (type 27) wherein R = OR^1, R^1 = H, S = U = H, T = OR^4, R^4 = alkyl, especially C_{1-4}alkyl, or alkenyl, V = OR^7, R^7 = COR^8, R^8 = alkyl, preferably C_{1-4}alkyl, especially methyl, W = H, X = CH_2OR^9, R^9 = COR^{10}, R^{10} = alkyl, especially C_{1-6}alkyl, alkenyl, especially C_{2-6}alkenyl, aryl or heteroaryl, Y = free electron pair and Z = CH_3, in which process a product of the process according to claim 45, 46 or 47 (type 26) is subjected to partial dealkylation or dealkenylation enzymatically and the compound of the general formula according to claim 1 having the indicated meanings is obtained.

49. Process according to claim 48, wherein an esterase, especially pig liver esterase, is used as the enzyme.

50. (Scheme 7) Process for the preparation of a compound of the general formula according to claim 1 (type 27) R = OR^1, R^1 = H, S = U = H, T = OR^4, R^4 = alkyl, especially C_{1-4}alkyl, or alkenyl, V = OR^7, R^7 = COR^8, R^8 = alkyl, preferably C_{1-4}alkyl, especially methyl, W = H, X = CH_2OR^9, R^9 = COR^{10}, R^{10} = alkyl, especially C_{1-6}alkyl, alkenyl, especially C_{2-6}alkenyl, aryl or heteroaryl, in which process
(a) in a first step
(i) a starting compound (type 1, 2 or 3) according to claim 3 or
(ii) a product of a process according to claim 15 (type 13)

is subjected to a process according to claim 45, 46 or 47 and
(b) in a second step a process according to claim 48 or 49 is carried out and the compound of the general formula according to claim 1 having the indicated meanings is obtained.

51. (Scheme 8) Process for the preparation of a compound of the general formula according to claim 1 (type 28 and, as the case may be, 29) wherein R = OR^1, R^1 = H, S = H or Hal, T = OR^4, R^4 = H, U = Hal, V = OR^7, R^7 = COR^8, R^8 = alkyl, preferably C_{1-4}alkyl, especially methyl, W = H, X = CH_2OR^9, R^9 = COR^{10}, R^{10} = alkyl, especially C_{1-6}alkyl, alkenyl, especially C_{2-6}alkenyl, aryl or heteroaryl, in which process
(i) a starting compound (type 1, 2, 3, 4, 5 or 6) according to claim 3 or
(ii) a product of a process according to claim 15 (type 13)
is subjected to halogenation or dihalogenation in the position ortho to the T substituent and the compound of the general formula according to claim 1 having the indicated meanings is obtained.

52. Process according to claim 51, wherein the halogenation is carried out in the presence of C_5Cl_5NF-triflate, SO_2Cl_2, NBS and ICl.

53. (Scheme 8) Process for the preparation of a compound of the general formula according to claim 1 (type 30) wherein R = OR^1, R^1 = H, S = H, T = OR^4, R^4 = H, U = NO_2, V = OR^7, R^7 = COR^8, R^8 = alkyl, preferably C_{1-4}alkyl, especially methyl, W = H, X = CH_2OR^9, R^9 = COR^{10}, R^{10} = alkyl, especially C_{1-6}alkyl, alkenyl, especially C_{2-6}alkenyl, aryl or heteroaryl, Y = free electron pair and Z = CH_3, in which process
(i) a starting compound (type 1, 2, 3, 4, 5 or 6) according to claim 3 or
(ii) a product of a process according to claim 15 (type 13)
is subjected to nitration in the position ortho to the T substituent and the compound of the general formula according to claim 1 having the indicated meanings is obtained.

54. Process according to claim 53, wherein the nitration is carried out using an alkali metal nitrite, especially sodium nitrite, and acetic acid in the presence of an organic solvent, especially ethanol.

55. (Scheme 8) Process for the preparation of a compound of the general formula according to claim 1 (type 31) wherein R = OR^1, R^1 = H, S = H, T = OR^4, R^4 = H, U = NH_2, V = OR^7, R^7 = COR^8, R^8 = alkyl, preferably C_{1-4}alkyl, especially methyl, W = H, X =

CH_2OR^9, $R^9 = COR^{10}$, R^{10} = alkyl, especially C_{1-6}alkyl, alkenyl, especially C_{2-6}alkenyl, aryl or heteroaryl, Y = free electron pair and Z = CH_3, in which process a product of a process according to claim 53 or 54 (type 30) is subjected to catalytic reduction and the compound of the general formula according to claim 1 having the indicated meanings is obtained.

56. Process according to claim 55, wherein the reduction is carried out using elemental hydrogen in the presence of palladium on activated carbon, especially in an organic solvent, preferably ethanol.

57. (Scheme 8) Process for the preparation of a compound of the general formula according to claim 1 (type 31) wherein R = OR^1, R^1 = H, S = H, T = OR^4, R^4 = H, U = NH_2, V = OR^7, $R^7 = COR^8$, R^8 = alkyl, preferably C_{1-4}alkyl, especially methyl, W = H, X = CH_2OR^9, $R^9 = COR^{10}$, R^{10} = alkyl, preferably C_{1-6}alkyl, alkenyl, especially C_{2-6}alkenyl, aryl or heteroaryl, Y = free electron pair and Z = CH_3, in which process
(a) in a first step
(i) a starting compound (type 1, 2, 3, 4, 5 or 6) according to claim 3 or
(ii) a product of a process according to claim 15 (type 13)
is subjected to a process according to claim 53 or 54 and
(b) in a second step the resulting product (type 30) is subjected to a process according to claim 55 or 56 and the compound of the general formula according to claim 1 having the indicated meanings is obtained.

58. (Scheme 8) Process for the preparation of a compound of the general formula according to claim 1 (type 32) wherein R = OR^1, R^1 = H, S = H, T = OR^4, R^4 = H, U = NHR^3, R^3 = alkyl-CO, especially C_{1-4}alkyl-CO, V = OR^7, $R^7 = COR^8$, R^8 = alkyl, preferably C_{1-4}alkyl, especially methyl, W = H, X = CH_2OR^9, $R^9 = COR^{10}$, R^{10} = alkyl, especially C_{1-6}alkyl, alkenyl, especially C_{2-6}alkenyl, aryl or heteroaryl, Y = free electron pair and Z = CH_3, in which process a product of a process according to claim 55, 56 or 57 (type 31) is subjected to alkylation and the compound of the general formula according to claim 1 having the indicated meanings is obtained.

59. Process according to claim 58, wherein the alkylation is carried out using an acid anhydride of formula $(R^3)_2O$ wherein R^3 = alkyl-CO, especially C_{1-4}alkyl-CO.

60. (Scheme 8) Process for the preparation of a compound of the general formula according to claim 1 (type 32) wherein R = OR^1, R^1 = H, S = H, T = OR^4, R^4 = H, U = NHR^3, R^3 = alkyl-CO, especially C_{1-4}alkyl-CO, V = OR^7, R^7 = COR^8, R^8 = alkyl, preferably C_{1-4}alkyl, especially methyl, W = H, X = CH_2OR^9, R^9 = COR^{10}, R^{10} = alkyl, especially C_{1-6}alkyl, alkenyl, especially C_{2-6}alkenyl, aryl or heteroaryl, in which process
(a) in an optional first step
(i) a starting compound (type 1, 2, 3, 4, 5 or 6) according to claim 3 or
(ii) a product of a process according to claim 15 (type 13)
is subjected to a process according to claim 53 or 54,
(b) in a second step the resulting product (type 30) is subjected to a process according to claim 55 or 56 and
(c) in a third step a process according to claim 58 or 59 is carried out and
the compound of the general formula according to claim 1 having the indicated meanings is obtained.

61. (Scheme 9) Process for the preparation of a compound of the general formula according to claim 1 (type 33) wherein R = OR^1, R^1 = H, S = U = H, T = OR^4, R^4 = H, V = OR^7, R^7 = COR^8, R^8 = alkyl, preferably C_{1-4}alkyl, especially methyl, W = H, X = CH_2OR^9, R^9 = COR^{10}, R^{10} = alkyl, especially C_{1-6}alkyl, alkenyl, especially C_{2-6}alkenyl, aryl or heteroaryl, Y = O and Z = CH_3, in which process
(i) a starting compound (type 1, 2, 3, 4, 5 or 6) according to claim 3 or
(ii) a product of a process according to claim 15 (type 13)
is subjected to a reaction for formation of an N-oxide and the compound of the general formula according to claim 1 having the indicated meanings is obtained.

62. Process according to claim 61, wherein the N-oxide formation is carried out using m-CPBA in an organic solvent, especially methylene chloride.

63. (Scheme 9) Process for the preparation of a compound of the general formula according to claim 1 (type 34) wherein R = OR^1, R^1 = H, S = U = H, T = OR^4, R^4 = H, V = OR^7, R^7 = COR^8, R^8 = alkyl, preferably C_{1-4}alkyl, especially methyl, W = H, X = CH_2OR^9, R^9 = COR^{10}, R^{10} = alkyl, especially C_{1-6}alkyl, alkenyl, especially C_{2-6}alkenyl, aryl or heteroaryl, Y = free electron pair, Z = COR^{11} and R^{11} = alkyl, preferably C_{1-4}alkyl, especially methyl, in which process the product of a process according to claim 61 or 62 (type 33) is reacted

with an acylating agent and the compound of the general formula according to claim 1 having the indicated meanings is obtained.

64. Process according to claim 63, wherein the acylation is carried out using an acid anhydride, especially acetic anhydride, preferably at elevated temperature.

65. (Scheme 9) Process for the preparation of a compound of the general formula according to claim 1 (type 34) wherein R = OR^1, R^1 = H, S = U = H, T = OR^4, R^4 = H, V = OR^7, R^7 = COR^8, R^8 = alkyl, preferably C_{1-4}alkyl, especially methyl, W = H, X = CH_2OR^9, R^9 = COR^{10}, R^{10} = alkyl, especially C_{1-6}alkyl, alkenyl, especially C_{2-6}alkenyl, aryl or heteroaryl, Y = free electron pair, Z = COR^{11} and R^{11} = alkyl, preferably C_{1-4}alkyl, especially methyl, in which process
(a) in a first step
(i) a starting compound (type 1, 2, 3, 4, 5, or 6) according to claim 3 or
(ii) a product of a process according to claim 15 (type 13) is subjected to a process according to claim 61 or 62 and
(b) in a second step the resulting product (type 33) is subjected to a process according to claim 63 or 64 and
the compound of the general formula according to claim 1 having the indicated meanings is obtained.

66. Therapeutic preparation, especially a cytostatic agent, comprising one or more compounds according to claim 1 or 2 as active ingredient in addition to one or more optional customary carriers and/or one or more optional customary diluents.

67. Therapeutic preparation, especially a cytostatic agent, comprising one or more products of a process according to one of claims 3 to 65 as active ingredient in addition to one or more optional customary carriers and/or one or more optional customary diluents.

68. Compound according to claim 1 or 2, wherein
alkyl is branched, unbranched or cyclic C_{1-20}alkyl, especially C_{1-7}alkyl, preferably C_{1-6}alkyl and more preferably C_{1-4}alkyl, especially methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, and cycloalkyl having preferably from 3 to 8 carbon atoms in the ring.

69. Compound according to claim 1, 2 or 68, wherein
alkenyl is branched, unbranched or cyclic C_{2-20}alkenyl, especially C_{2-7}alkenyl, preferably C_{2-6}alkenyl and more preferably C_{2-4}alkenyl, especially vinyl, allyl, propen-1-yl, propen-2-yl, but-1-en-1-yl, but-1-en-2-yl, but-1-en-3-yl, but-1-en-4-yl, but-2-en-1-yl, but-2-en-2-yl, 2-methyl-propen-1-yl, 2-methyl-propen-3-yl, and cycloalkenyl having preferably from 3 to 8 carbon atoms in the ring and the number of double bonds in the alkenyl groups being from 1 to 3.

70. Compound according to claim 1, 2, 68 or 69, wherein
aryl is phenyl, naphthyl and biphenylyl.

71. Compound according to claim 1, 2, 68, 69 or 70, wherein
heteroaryl is furyl, thienyl, imidazolyl, indolyl, pyridyl, pyridinyl, pyrrolyl, thiazolyl, oxazolyl or pyrimidinyl.

72. Compound according to claim 1, 2, 68, 69, 70 or 71, wherein
alkyl, alkenyl, aryl and heteroaryl are unsubstituted or substituted and, especially, carry, in any position, from 1 to 3 substituents from the group formed by C_{1-3}alkyl, C_{1-3}alkoxy, hydroxy, amino (NH_2) and nitro (NO_2).